Application Ser. No.: 10/511,886
Filing Date: October 19, 2004
Examiner: Perlinger, Sarah E

Remarks

In the Office Action, the Examiner noted that claims 1-3 and 5-16 are pending in the application; and that claims 1-3 and 5-16 are rejected. By this amendment, claim 1 has been amended, new claims 17-38 have been added and claims 12-16 have been cancelled without prejudice or disclaimer of the subject matter contained therein. Thus, claims 1-3, 5-11 and 17-38 are pending in the application. No new subject matter has been inserted through these amendments.

All of the amendments are fully supported by the specification. For instance, claim 1 was amended to address 35 U.S.C. § 112, second paragraph issues and to recite various substituents with better clarity. New claim 17 recites a narrower scope of compound of claim 1. New claims 18-21 recite some of the specific compounds disclosed throughout the specification, more specifically, in Examples 1-8 of the specification at pages 11-31 and the Tables 1 and 2 summarized thereafter at pages 32-38 of the specification. New claims 22-25 recite pharmaceutical compositions of compounds of new claims 18-21. Finally, new claims 26-29, 34 and 35 recite method of treatment using the compounds of claims 1, 2, 3, 6 and 7 and are similar in scope to those of cancelled claims 12-16, but are re-written in better form to overcome the outstanding rejections under 35 U.S.C. § 112, first paragraph and to place them in condition for allowance. Similarly, new claims 30-33 and 36-38 recite method of treatment using the compounds of new claims 17-21. The Examiner's rejections are respectfully traversed below.

Oath/Declaration

The Examiner has noted that the oath/declaration submitted with the instant application is defective. Accordingly, Applicants submit concurrently herewith a duly executed new oath/declaration. Further, it is respectfully submitted that this duly executed oath/declaration is fully in compliance with 37 CFR 1.67(a). Thus, entry of this new oath/declaration into record is respectfully requested.

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Specification

The Examiner has further noted that the title on page 1 of the specification is underlined by hand, thus appropriate correction is requested. As noted, by way of this amendment, Applicants are requesting the Examiner to delete the current title at page 1 of the specification and insert therefor the title provided in this amendment in accordance with 37 CFR 1.121.

The Examiner has also objected to the abstract as it is considered to be longer than one page. Again, as noted, a new abstract has been provided in this amendment on a separate page (see page 3 of this response) pursuant to 37 CFR 1.72 and in accordance with 37 CFR 1.121. Please note that this is being submitted as a new abstract and requesting the Examiner to delete the abstract on record and replace it with this newly submitted abstract. Accordingly, withdrawal of this objection is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-3, 5, 8-9 and 12-14 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner has alleged that the scope of claims 1-3, 5, 8-9 and 12-14 cannot be ascertained due to the ambiguity of the phrase, a compound in the form of a "pure optical isomer." It is respectfully submitted that claim 1, as amended, fully satisfies the requirements of 35 U.S.C. § 112, second paragraph, and thus obviating this rejection.

Specifically, the objected term, "pure optical isomer" appears only in independent claim 1. However, claim 1 has been amended to delete this term and a term "an enantiomer" is used instead. Support for this can be found at various places of the specification, and more particularly at page 2, lines 15-17. It is further submitted that one of ordinary skill in the art readily appreciates the intended meaning of an enantiomer is being a single optically pure isomer. Accordingly, withdrawal of rejection as to claims 1-3, 5, 8-9 and 12-14 is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 12-16 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner alleges that the scope of claims 12-16 cannot be ascertained due to the ambiguity of the phrase, a method for the treatment of disorders in which glycine transporters "are involved." However, claims 12-16 have been cancelled without prejudice, thus obviating this rejection.

Instead, new claims 26-38 are presented in this amendment all of which recite method of treatment of a disorder associated with either a glyt1 or glyt2 transporter. Accordingly, it is submitted that new claims 26-38 fully satisfy the requirements of 35 U.S.C. § 112, second paragraph, as they are drawn to method of treatment of a disorder associated with either glyt1 or glyt2 using the compounds of the instant invention. Specific details of discussion of these claims are further given below. Therefore, withdrawal of rejection as to claims 12-16 is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 12-16 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

In particular, the Examiner asserts that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. However, as noted, Applicants have cancelled claims 12-16 obviating this rejection.

New claims 26-38 are redrawn to show specific disorders that can be treated by the inhibition of glyt1 transporters (claims 26-33) or by glyt2 transporters (claims 34-38) using respective compounds of this invention. It should further be noted that there is clear written description for said treatments. See for instance, page 3, lines 6-12 where it is shown clearly preferred compounds that can be used for either of the glyt1 or glyt2 inhibition. Biological test methods, for instance study of glyt1 inhibition is fully

described beginning at page 39, line 8 to line 19, page 40. *Ex vivo* animal models to test the efficacy of the compounds of the invention in inhibiting glyt1 is shown on pages 40 and 42. Similar studies to test the biological efficacy of the compounds of the invention in glyt2 inhibition is shown in test methods presented on pages 42-44. Further summary of these studies is provided in pages 45-46 of the specification. In view of the foregoing, it is respectfully submitted that new claims 26-38 fully satisfy the requirements of 35 U.S.C. § 112, first paragraph. Accordingly, withdrawal of rejection as to claims 12-16 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-3 and 5-11 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Kikuchi et al. (EP 0 499 995) in view of Froelich et al. (J. Org. Chem., 1996, 61, 6700-6705) or Cheeseman et al. (US 5,254,569).

The Examiner alleges that "Kikuchi et al. and Cheeseman et al. disclosed generically the claimed anti-psychotic compounds and pharmaceutical compositions against the base claims as delineated. Explicit compounds are guided by the reference (Cheeseman et al., Table 1, example 53) and render the claimed compounds generically encompassed."

Applicants respectfully submit that the Examiner has erred in her analysis and as it becomes apparent from the detailed discussions that follow, claims 1-3 and 5-11 are neither taught nor suggested by Kikuchi et al. in view of Froelich et al. or Cheeseman et al. Thus, it is respectfully submitted that claims 1-3 and 5-11 are patentably distinguishable over Kikuchi et al. in view of Froelich et al. or Cheeseman et al. Accordingly, withdrawal of rejection as to claims 1-3 and 5-11 is respectfully requested.

For instance, Kikuchi et al. disclose a series of piperidine derivatives, which are different from the compounds of the instant invention. The Examiner's attention is particularly drawn to the general scope of the structure of the compounds of formula (I) disclosed at pages 3 and 4 of Kikuchi et al. More particularly, Kikuchi et al. describe primarily a series of piperidine containing carboxylic acid esters, including only one

specific amide. This generic structure does encompass piperidinyl benzamide derivatives as correctly pointed out by the Examiner, but with only one example.

However, it is again respectfully submitted that the compounds of the present invention are different from the ones described in Kikuchi et al. because of the fact that the compounds of the present invention contain a "a trifluoromethyl (CF_3) group" on the phenyl ring. Even more importantly, as admitted by the Examiner, the compounds of the present invention are optically pure stereospecific enantiomers or threo diastereoisomers as recited in claim 1, as amended. Please further note that there is only one specific example of an amide in Kikuchi et al., see for example, "1-(1-ethyl-2-piperdinyl)ethylindole-3-carboxamde," at line 2, page 5 of Kikuchi et al., and rest of the specific compounds synthesized therein are esters, again see, line 48, page 4 to line 3, page 5 of Kikuchi et al.

However, the Examiner alleges that Kikuchi et al. disclose "generic teaching on the piperidinyl benzamide stereoisomers and their mixtures and racemates," citing Kikuchi et al. at page 4, lines 42-43. However, it should be reiterated that the compounds of Kikuchi et al. are different from the compounds of the present invention and Kikuchi et al. make a generic statement with no specific example, as also noted by the Examiner. Thus, in spite of structural differences as pointed out above no specific piperidinyl benzamides are disclosed in Kikuchi et al., let alone mention of the synthesis of stereospecific threo diastereoisomers and/or about specific mention of the enantiomers, (1R, 2R) or (1S, 2S) as presently taught in the instant invention and specifically claimed in claims 1-3 and 5-11.

It should also be noted that the compounds of Kikuchi et al. are selective antagonists of 5-hydroxytryptamine (5-HT) at 5-HT_3 receptors thus exhibiting anti-psychotic activity, see specifically at lines 31-32, page 3 of Kikuchi et al. More importantly, there is no structure activity relationship (SAR) provided in Kikuchi et al. such that it would motivate one of ordinary skill in the art of medicinal chemistry to make the structural modifications so as to arrive at the compounds of the instant invention, at the time the Applicants made this invention, and to use such compounds as inhibitors of

glycine transporters, such glyt1 or glyt2, as currently taught by the Applicants. Thus, it is submitted that claims 1-3 and 5-11 are patentably distinguishable from Kikuchi et al.

As to Cheeseman et al., they disclose a series of (amidomethyl)nitrogen heterocyclic analgesics. Again, the compounds of Cheeseman et al. are structurally different from the compounds of the instant invention. Similarly, Froelich et al. teach an asymmetric synthesis of 2-(1-aminoalkyl)piperidines, which are distinctively different classes of compounds than the ones described in the instant invention except that it describes certain asymmetric synthesis of piperidine compounds. However, there is no structural relevance to the compounds of the present invention. More importantly, there is no teaching or suggestion in Cheeseman et al. and/or Froelich et al. so as to motivate one of ordinary skill in the art to arrive at the compounds of the present invention at the time Applicants made this invention.

In view of the foregoing it is respectfully submitted that claims 1-3 and 5-11 are patentably distinguishable over combined teachings of Kikuchi et al. in view of Froelich et al. or Cheeseman et al. Accordingly, withdrawal of rejection as to claims 1-3 and 5-11 is respectfully requested.

First of all, Applicants respectfully submit that the Examiner erred in concluding that there is enough motivation from the disclosures of Kikuchi et al. to arrive at the Applicants' invention at the time the Applicants made this invention. In particular, claims 1-3 and 5-11 recite a series of stereospecifically substituted piperidinyl benzamide compounds, none of which is taught or suggested by Kikuchi et al., as evidenced by the above arguments. Even more importantly, the compounds of claims 1-3 and 5-11 are useful as either inhibitors of glyt1 or glyt2 transporters whereas compounds of Kikuchi et al. are useful as antipsychotic agents. One skilled in the art of medicinal chemistry readily appreciates this to be a vastly different utility having different structure activity relationships (SAR) at the relevant receptor site, contrary to the views of the Examiner.

As we already noted above, it should be reiterated that there is no teachings of the SAR of various piperidinyl compounds as disclosed in Kikuchi et al. such that one of ordinary skill in the art could ascertain activities of various substituted piperidinyl

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derivatives in the antipsychotic activity let alone activity at the glyt1 or glt2 transporters as presently taught in the instant invention. To the contrary, the Examiner simplistically and incorrectly concludes that:

> "...the generic disclosure by Kikuchi et al. fully encompassed the instant scope, and the specific teaching by Froelich et al. to separate the optical isomers of structurally analogous compounds would render the threo diastereoisomer and optically pure form of the compounds obvious. One having ordinary skill in the art would be motivated to make such modification of separating the optical isomers, knowing that the biological system in stereospecific."

Applicants respectfully submit that Examiner has erred in arriving at this conclusion based on both legal and scientific grounds.

It is well known scientific principle that the reactivity of an organic molecule, such as piperidinyl derivative as described in the present invention, differs vastly depending upon the substituents it contains. This is especially true when there is no well established SAR as we stated above and especially when the uses are of vastly different involving totally different receptor sites – antipsychotic vs. glycine transporter. Thus, contrary to the assertion of the Examiner, a person of ordinary skill in the art would have had no motivational basis to arrive at the present invention simply following the teachings of Kikuchi et al. in view of Froelich et al. or Cheeseman et al. at the time Applicants made the instant invention. As stated in a leading organic text book:

> ".....it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is part of. The reaction at the functional group is influenced by the rest of the molecule. This influence *may be great enough to stop the reaction completely* or to make it *take an entirely unexpected course*. Even when *two compounds with the same functional group undergo the same reaction*, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the

structures of the compounds. *The greatest variations may be expected when additional functional groups are present.*[1]" (emphasis added)

From this it is clear that a skilled artisan would not have been motivated by the teachings of Kikuchi et al. to arrive at the present invention. This is especially true when there is no teaching of the type of compounds of the instant invention in Kikuchi et al. Even more importantly, the Board has held that in an obviousness determination the prior art must provide some impetus for the one of ordinary skill in the art to arrive at the present invention. As stated by the Board:

> At best, the Examiner's comments regarding obviousness amount to an assertion that one of ordinary skill in the relevant art would have been able to arrive at appellant's invention because he had the necessary skills to carry out the requisite process steps. *This is an inappropriate standard for obviousness*....That which is within the capabilities of one skilled in the art is not synonymous with obviousness....That one can reconstruct and/or explain the theoretical mechanism of an invention by means of logic and sound scientific reasoning does not afford the basis for an obviousness conclusion *unless that logic and reasoning also supplies sufficient impetus to have led one of ordinary skill in the art to combine the teachings of the references to make the claimed invention*[2] (emphasis added).

From the foregoing discussions it is clear that there is neither logic nor sound scientific reasoning that provides sufficient impetus for one of ordinary skill in the art to arrive at the present invention merely following Kikuchi et al. in view of Froelich et al. or Cheeseman et al. That is, because of the fact that various substituents as recited in claim 1 would exert different electronic effect to the piperidine benzamide molecule, it is highly unlikely that a person of ordinary skill in the art would believe that all of the substituents

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[1] Advanced Organic Chemistry, Chapter 9, "Effects of Structure on Reactivity", p 237, J. March, 3rd Ed., John Wiley & Sons, 1985.

[2] Ex parte Levengood, 28 USPQ2d 1301-02 (Bd. Pat. App. & Inter. 1993); a somewhat similar result was reached by the court in *In re Brouwer* holding that the claim under examination may not be rejected under

would behave the same way and use it either as antipsychotic compound as taught by Kikuchi et al. or as glycine transporter as taught in the instant invention – different utilities and properties of different compounds. Thus, the Examiner erred in concluding that there was enough motivation to arrive at the present invention following the teachings of Kikuchi et al. in view of Froelich et al. or Cheeseman et al.

In view of all of the arguments advanced above, Applicants respectfully submit that claims 1-3 and 5-11 as well as new claims 17-25 are patentably distinguishable over Kikuchi et al. in view of Froelich et al. or Cheeseman et al. Therefore, withdrawal of rejection as to claims 1-3 and 5-11 is respectfully requested.

Double Patenting Rejection

Claims 1-3, 5, 8-9 and 12-14 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 of copending Application No. 11/045,247.

Applicants submit that since this is a provisional rejection, upon allowance of either or both of the subject applications a terminal disclaimer will be filed.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 1-3, 5-11 and 17-38 are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

As noted above, Applicants concurrently submit herewith a petition for one-month extension of time to make this response timely. Applicants request the Commissioner to charge these fees and any other fees that are deemed necessary due to

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35 U.S.C. § 103 unless the prior art suggested the desirability of such a modification as claimed: see In re Brouwer, 77 F.3d 422, 37 USPQ 2d 1663 (Fed. Cir. 1966).

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this submission to Deposit Account No. **18-1982** for sanofi-aventis U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982.**

Respectfully submitted,

May 17, 2006

Balaram Gupta

Balaram Gupta, Ph. D., J. D.
Registration No. 40,009
Attorney for Applicants

Enclosure: Petition for one-month extension of time under 37 CFR 1.136(a) (1 page)
A copy of duly executed oath/declaration (6 pages)

sanofi-aventis U.S. LLC
US Patent Operations
Route #202-206 / P.O. Box 6800
MAIL CODE: BWD-303A
Bridgewater, NJ 08807-0800
Telephone: 908-231-3364
Telefax: 908-231-2626